

Remarks

Applicants have amended Figures 1A-10 herein to address the problems noted in the Notice of Draftsperson's Patent Drawing Review. The amended figures are attached. In addition, Applicants removed material that might be considered descriptive since they were required to do so in the parent application. The specification was amended to incorporate the material that was removed from the drawings. No new matter was added by the amendments to the specification or drawings. Applicants respectfully urge that the drawings as now presented be entered.

Claims 26-35, 46-50, 61-63, 70, 71, and 73-97 are pending in the application. Claims 26-35, 50, 61-63, 84, 86-93, and 95-97 are withdrawn. Claims 46-49, 70-71, 73-83, 85 and 94 stand rejected. Claims 46 and 74-83 are amended herein. Claims 46 and 83 were amended to specify that the methods are directed to delivery of the drug-oligomer conjugates across the blood brain barrier. Claims 74-82 were amended to clarify that administration was to the subject. Support for these amendments can be found throughout the specification and claims as originally filed. No new matter was added by the amendments, and Applicants respectfully request their entry.

I. Claim Rejections – 35 U.S.C. § 103

A. The Examiner has rejected claims 46-49, 70-71, 73-83, and 85 under 35 U.S.C. § 103(a) as being allegedly unpatentable over Yagi et al. (US Patent No. 5,061,691) and Ekwuribe (US Patent No. 5,681,811). Applicants respectfully traverse this rejection.

The Examiner states that Yagi teach the induction of analgesia by opioids and the making of analogs of the peptide opioids Met- and Leu-enkephalins in order to promote *in vivo* delivery by overcoming administration obstacles. See abstract; col. 1; and patent claims. The Examiner further states that the Yagi reference differs from the present invention, which achieves analgesic therapy of opioids by conjugating them with a polymer which comprises lipophilic and hydrophilic moieties. The Examiner then states that Ekwuribe teaches the stabilization of “therapeutic agents” for *in vivo* administration by conjugating with a polymer which comprises lipophilic and hydrophilic moieties, and that the therapeutic agents are preferably opioids, especially peptidic opioids. The Examiner argues that one of ordinary

skill in the art would have been motivated to conjugate opioids, especially peptide opioids Met- and Leu-enkephalins and analogs thereof, as disclosed in Yagi in the manner of Ekwuribe to achieve the analgesic composition overcoming the *in vivo* obstacles recited in Yagi.

To establish a *prima facie* case of obviousness, three basic criteria must be met. The prior art reference (or references when combined) must teach or suggest all the claim limitations. There must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings, and there must be a reasonable expectation of success in the combination. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. See MPEP § 2143. Applicants respectfully submit that these criteria have not been met.

Ekwuribe (US Patent No. 5,681,811) does not teach or suggest Applicants' invention. Applicants have amended independent claims 46 and 83 to specify that the methods are directed to delivery of the drug-oligomer conjugates across the blood brain barrier. In contrast, Ekwuribe appears to be directed to "chemical modification that will allow penetration of the attached peptide, e.g., insulin, through cell membranes." (Column 11, lines 26-28). Ekwuribe notes that such chemical modification of insulin, for example, will "improve the intestinal absorption of insulin." Applicants respectfully submit that the ability of a conjugate to cross the blood-brain barrier as recited in claims 46 and 83 is far different from the ability of a conjugate to cross a cell membrane as proposed by Ekwuribe. As noted in PRINCIPLES OF NEURAL SCIENCE 1054 (Eric R. Kandel et al., eds., 3d ed., 1991):

Using electron microscopy and electron-dense tracers such as horseradish peroxidase (HRP) and lanthanum, Morris Karnovsky and Thomas Reese demonstrated that the blood-brain barrier of vertebrates is located in the specialized endothelial cells of the capillaries in the brain. These capillaries of the brain consist of overlapping endothelial cells that make frequent contact on their abluminal (brain) side with projections from *astrocytes*, referred to as glial end-feet.

The endothelial cells of the capillaries in the brain differ from those in other organs in two important ways. These differences account for the ability of the blood-brain barrier to exclude certain molecules. First, peripheral endothelial cells are either fenestrated or have tight junctions of low resistance ($5/10 \text{ ohm}\cdot\text{cm}^2$) between the cells. In contrast, brain endothelial cells are joined by tight junctions of high electrical resistance ($1000 \text{ ohm}/\text{cm}^2$ or more). These high resistance junctions present an effective barrier even to ions. Thus, in brain there is little movement of compounds between endothelial cells.

Second, in peripheral endothelial cells there is good transcellular movement of compounds. In contrast, there is no such transport through brain endothelial cells. In peripheral endothelial cells, molecules move across the cells by two means: (1) *fluid-phase endocytosis*, a relatively nonspecific process in which endothelial cells (and most other cells) first engulf molecules encountered in the extracellular environment and then internalize the molecules by means of vesicular endocytosis; and (2) *receptor-mediated endocytosis*, a specific process in which a ligand first binds to a membrane receptor on one side of the cell. After binding, the complex is internalized into a vesicle and transported across the cell, and the ligand may be released. Endothelial cells of the brain lack both of these mechanisms. Thus, the physiology of a cell membrane (e.g., a peripheral endothelial cell) is far different from the physiology of the blood-brain barrier. Accordingly, Applicants submit that it would not be obvious to provide the claimed conjugates that are capable of crossing the blood-brain barrier in view of the disclosure of Ekwuribe (US Patent No. 5,681,811), which proposes conjugates capable of crossing cell membranes.

Further, Applicants direct the Examiner to statements made by Examiner MacMillan in the parent application (US Appln. No. 09/134,803) with respect to Ekwuribe (US Patent No. 5,681,811). In paper number 11, dated 01/20/00, page 2, under the heading "Allowable Subject Matter," Examiner Macmillan stated:

Ekwuribe, in US patent 5,681,811, teaches polyoxyethylene cetyl ether reaction products can be formed with a variety of drugs, including insulin, enkephalins, vasopressin, endorphins, etc. The conjugates may be used, according to the patent, as drug delivery vehicles. There is no suggestion in the reference that the resulting conjugates may be used to deliver such drugs across the blood brain barrier (BBB), however, given the unpredictability with

respect to this art, it would not have been obvious that such conjugates would be capable of trans-BBB delivery, absent a teaching to the contrary.

Thus, it is clear that the disclosure of Ekwuribe does not teach or suggest the invention claimed herein.

Furthermore, Yagi et al. (US Patent No. 5,061,691) does not teach or suggest Applicants' invention nor does Yagi provide any motivation for combining the teachings of Ekwuribe and Yagi. Applicants respectfully submit that the Examiner has mischaracterized the teachings of Yagi. Column 1, paragraph 4, of Yagi reads, in pertinent part: "The molecular structure of synthetic enkephalins has been designed to yield enkephalins with the following characteristics: ... e) ability to pass through the blood-brain barrier..." Thus, what Yagi teaches is that the synthetic enkephalins are known to cross the blood-brain barrier. Therefore, this reference provides no motivation for one skilled in the art to seek ways to modify enkephalin to facilitate crossing the blood-brain barrier.

Further, Yagi's invention is directed to enkephalin analogs that can already cross the blood brain barrier without conjugation to any other compounds. Thus, not only does Yagi provide no teaching or suggestion that the enkephalin analogs need to be modified to cross the blood-brian barrier, but Yagi actually teaches away from conjugating enkephalins. The Court of the Federal Circuit has determined that it is erroneous to arrive at a finding of obviousness where the references "diverge from and teach away from the invention at hand," *In re Fine*, 5 U.S.P.Q.2d 1596 (Fed. Cir. 1988), which is the situation of the Yagi reference.

Thus, it is apparent that neither Ekwuribe nor Yagi either alone or in combination would have rendered the claimed invention obvious. Therefore, Applicants respectfully request withdrawal of the rejection.

B. The Examiner has rejected claims 46-49, 70-71, 73-83, 85, and 94 under 35 U.S.C. § 103(a) as being allegedly unpatentable over Yagi et al. (US Patent No. 5,061,691) and Ekwuribe (US Patent No. 5,681,811) and further in view of Mensi-Fattohi et al. (US Patent No. 5,428,128).

Applicants reiterate the arguments regarding Ekwuribe and Yagi presented above. Additionally, Applicants respectfully submit that the Examiner has not pointed to anything that would motivate a person skilled in the art to modify the teachings of Mensi-Fattohi or to

combine those teachings with the teachings of Ekwuribe to arrive at the current invention. In particular the Examiner appears to reject claim 94 as obvious in view of the previously discussed references in combination with Mensi-Fattohi. The Examiner states that Mensi-Fattohi teaches the carbamate attachment of PEG to opioid peptides through a lysine epsilon amino group in which the lysine is initially present or subsequently added to the opioid peptide. The Examiner further states that it would have been *prima facie* obvious to one of ordinary skill in the art at the time of Applicant's invention to further modify the enkephalin (e.g. Met-enkephalin) containing PEG-alkyl conjugates to attach (via a carbamate bond) by the use of a lysine epsilon amino group as taught by Mensi-Fattohi in light of the Ekwuribe teaching of using amino groups for carbamate PEG attachment. There is no teaching or suggestion in the Mensi-Fattohi or in any combination of the references to produce the specific oligomer of claim 94.

As recently affirmed by the Court of Appeals for the Federal Circuit, to support combining references in a § 103 rejection, evidence of a suggestion, teaching, or motivation to combine must be clear and particular, and this requirement is not met by merely offering broad, conclusory statements about teachings of references. *In re Dembicza*k, 50 USPQ2.d 1614, 1617 (Fed. Cir. 1999). Thus, Applicants believe that this rejection is overcome and respectfully request its withdrawal.

II. Rejection under judicially created doctrine of obviousness-type double patenting

A. The Examiner has rejected claims 46-47, 70-71, and 73-82 under the judicially created doctrine of obviousness-type double patenting doctrine as being allegedly unpatentable over claims 1-60 of US Patent No. 6,309,633 and Yagi et al. (US Patent No. 5,061,691).

Applicants will submit a terminal disclaimer, if necessary, to obviate the double patenting rejection upon notification of allowable subject matter. Applicants note that the submission of this terminal disclaimer in no way represents acquiescence to the outstanding rejection or an acknowledgement that the subject matter of the pending claims is obvious

over the cited claims of US Patent No. 6,309,633. Additionally, Applicants reiterate the arguments presented above regarding Yagi.

B. The Examiner has rejected claims 46-49, 70-71, 73-83, 85, and 94 under the judicially created doctrine of obviousness-type double patenting doctrine as being allegedly unpatentable over claims 1-60 of US Patent No. 6,309,633 and Yagi et al. (US Patent No. 5,061,691) in view of Ekwuribe (US Patent No. 5,681,811) alone and further in view of Mensi-Fattohi et al. (US Patent No. 5,428,128).

Applicants will submit a terminal disclaimer, if necessary, to obviate the double patenting rejection upon notification of allowable subject matter. Applicants note that the submission of this terminal disclaimer in no way represents acquiescence to the outstanding rejection or an acknowledgement that the subject matter of the pending claims is obvious over the cited claims of US Patent No. 6,309,633. Additionally, Applicants reiterate the arguments presented above regarding Ekwuribe (US Patent No. 5,681,811), Yagi, and Mensi-Fattohi.

C. The Examiner has rejected claims 46-49, 70-71, 73-83, and 85 under the judicially created doctrine of obviousness-type double patenting doctrine as being allegedly unpatentable over claims 1-44 of Ekwuribe (US Patent No. 5,681,811) and Yagi et al. (US Patent No. 5,061,691).

Applicants reiterate the arguments presented above in support of the position that the claimed invention is not obvious in view of these references either alone or in any combination. Thus, Applicants respectfully request withdrawal of this rejection.

D. The Examiner has rejected claims 46-49, 70-71, 73-83, 85, and 94 under 35 U.S.C. § 103(a) as being allegedly unpatentable over Ekwuribe (US Patent No. 5,681,811) and Yagi et al. (US Patent No. 5,061,691) as applied to 46-49, 70-71, 73-83, and 85 above, and further in view of Mensi-Fattohi et al. (US Patent No. 5,428,128).

Applicants reiterate the arguments presented above in support of the position that the claimed invention is not obvious in view of these references either alone or in any combination. Thus, Applicants respectfully request withdrawal of this rejection.

E. The Examiner has rejected claims 46-49, 70-71, 73-83, and 85 under the judicially created doctrine of obviousness-type double patenting doctrine as being allegedly unpatentable over the claims (e.g. claims 46-52) of Ekwuribe et al. (US Appl. No. 09/429,798).

The current application and US Appl. No. 09/429,798 are each divisional applications of US Appl. No. 09/134,803. US Appl. No. 09/134,803 was subject to a restriction requirement mailed on October 1, 1999 that divided the claims into five groups. Group III was elected for the parent application. Group I was filed in US Appl. No. 09/429,798. Groups II, IV and V were filed in the current application. According to 35 U.S.C. § 121:

A patent issuing on an application with respect to which a requirement for restriction under this section has been made, or on an application filed as a result of such a requirement, shall not be used as a reference either in the Patent and Trademark Office or in the courts against a divisional application or against the original application or any patent issued on either of them, if the divisional application is filed before the issuance of the patent on the other application.

Applicants respectfully submit that this rejection was made in error and, therefore, should be withdrawn.

F. The Examiner has rejected claims 46-49, 70-71, 73-83, 85, and 94 under 35 U.S.C. § 103(a) as being allegedly unpatentable over Ekwuribe et al. (US Appl. No. 09/429,798) as applied to claims 46-49, 70-71, 73-83, and 85 above, and further in view of Ekwuribe (US Patent No. 5,681,811) and Mensi-Fattohi et al. (US Patent No. 5,428,128).

Applicants reiterate the arguments presented above with respect to US Appl. No. 09/429,798 and respectfully request withdrawal of this rejection.

Applicants respectfully submit that the claims and drawings as now presented are in form for allowance and request that a Notice of Allowance be issued. The Examiner is encouraged to contact the undersigned directly if such contact will expedite the examination and allowance of the pending claims.

Attorney Docket No. 92353DV2

In re: Ekwuribe et al.

Appl. Serial No.: 09/430,735

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Page 22 of 22

A check in the amount of \$110.00 is enclosed for the one month extension fee. This amount is believed to be correct, however, the Commissioner is hereby authorized to charge any deficiency or credit any overpayment to Deposit Account No. 50-0220.

Respectfully submitted,



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